REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 332-355 were presented as new claims in the Amendment of April 10, 2003. Claims 332-355 are now the only claims in the case.

I. THE COMMUNICATION DATED AUGUST 6, 2003

The Communication mailed August 6, 2003 asserts that the response dated April 10, 2003 is not fully responsive to the final rejection mailed February 10, 2003. In response, the present Response repeats the points made in the Response dated April 10, 2003 and, in addition, specifically addresses each of the rejections in the final rejection of February 10, 2003.

II. THE INTERVIEW OF MARCH 28, 2003

The undersigned wishes to thank the Examiner (Ms. Scheiner) and her supervisor (Mr. Housel) for their time and consideration of the issues during the personal interview of March 28, 2003 and the telephone interviews on September 5, 2003. As noted in the Interview Summary Record, it was agreed that the finality of the Official Action dated February 10, 2003 would be withdrawn. Further, the Examiners expressed a high likelihood that the subject matter of claims 332 and 333 (now claims 332-355) would be rejoined to the elected invention.

Applicants agreed to submit evidence of enablement by providing data on additional viral strains, as well as evidence relating to local versus systemic administration.

Claims which the Examiner stated were elected in paper 31 page 2 (or also paper 48 page 2), were reintroduced in the Amendment dated December 6, 2002:

Claim 332 is similar to old claim 164; and

Claim 333 is similar to old claim 177.

Support for amended claim 333 (and claims 334-346 and 344-347) can be found on pages 11, 12 and 13 of the originally-filed specification.

Independent claim 343 and its dependent claims, also relate to a method of treating cancer by systemic administration of NDV, but additionally require more than one dose of the virus. Independent claim 355 relates to a method of treating cancer in a mammal having a tumor comprising administering intravenously to said mammal more than one dose of a Newcastle Disease Virus an amount sufficient to cause tumor regression. Basis for administration of more than one dose of the virus appears, for example, at the bottom of page 13 of the specification.

Claims 332-355 presented with the Amendment of April 10, 2003 do not constitute the introduction of new matter. Entry and favorable consideration of claims 332-355 based on the comments presented below are respectfully requested.

III. PREVIOUS CLAIM 318

On page 2 of the action, the Examiner has quoted the second paragraph of 35 USC 112, and has asserted that the term "moderate" allegedly renders the claim indefinite. In response, and without conceding to the merit of this assertion, the term "moderate" does not appear in claims 332-355.

IV. THE 35 USC 112, FIRST PARAGRAPH, REJECTIONS

Claims 318, 320, 322, 323 and 328 stand rejected under 365 USC 112, first paragraph, on alleged lack of enablement grounds. Claims 318, 320, 322, 323 and 328 also stand rejected under 365 USC 112, first paragraph, as drawn to subject matter

allegedly not described in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

In response, and without conceding to these rejections, claims 318, 320, 322, 323 and 328 have been canceled without prejudice. The lack of enablement and written description requirement rejections with respect to those claims have accordingly been rendered moot.

For the reasons discussed below, it is believed that currently pending claims 332-355 are enabled by the specification, and also satisfy the written description requirement of 35 USC 112, first paragraph. During the interview on March 28, 2003, the Examiners suggested that it would be helpful, in considering the applicability of the outstanding rejections to the new claims to be presented (claims 332-355) to provide a brief summary of the history of the rejections in the case as they pertained to claims similar to the currently pending claims. This summary is presented below, from which it will be clear that claims 332-355 are in full compliance with enablement and written description requirements of 35 USC 112, first paragraph.

Prior Rejections of Claims 164, 165, 167, 168 and 177

Lack of Enablement

In the Official Action of May 26, 1998, page 3, the Examiner rejected claims 164, 165, 167, 168 and 177 under 35 USC 112 first paragraph on alleged lack of enablement grounds. The Examiner alleged that "the specification teaches only the use of NDV 73-T strain which is not sufficiently enabling for all NDV strains, or any mesogenic strain."

The Examiner also alleged that "systemic administration has not been taught in the specification (claims 164-168)."

Newcastle Disease Virus (NDV)

The subject patent application specifically describes by way of exemplification *two* NDV strains to treat cancer (Mass MK 107 and 73-T). In the specification, there is an example (Example 3, page 27 along with Figure 5) of tumor regression using an NDV strain other than 73-T: the strain Mass MK107. Mass MK107 is a well-known NDV strain.

Further support that the disclosure made in the subject application regarding NDV is enabling can be found in commonly owned U.S. Serial No. 09/292,376, (now U.S. Serial No 10/167,652) where there are examples of antitumor efficacy with two other strains of NDV in Examples 21, 22, 23. This is in addition to the extensive examples (Examples 1-10, 16-17, 29 and including an example with human clinical data - Example 20) that used Mass MK107, the mesogenic strain of NDV.

This evidence of successful results with additional strains of NDV confirms the statement of applicants in the subject application that NDV generally, and not just the exemplified strains, can be used in accordance with the claimed method.

Systemic Administration

The term "systemically" is supported and described in the specification on page 13: "the virus can be administered either directly at the tumor site by local or regional injection, or systemically." See also Example 2 relating to systemic NDV therapy leading to pronounced antitumor effects. Example 2 of the specification further indicates that "NDV is effective at treating cancer when administered systemically."

Intravenous and intraperitoneal administration are described in the subject specification (see, page 13 first full paragraph: "The virus is preferably administered to the mammal by injection (e.g. intravenous...intraperitoneal....)"

Further support that the disclosure made in the subject application regarding intravenous administration is enabling can be found in commonly owned Serial No. 09/292,376 (now U.S. Serial No 10/167,652), where additional examples are provided of antitumor efficacy using the intravenous route with mesogenic MK107 strain: Examples 3, 9 and 20 (with Example 20 showing clinical human experience of systemic treatment including regressions of 5 tumors). In this regard, attention is directed to the 2002 article by Pecora et al entitled "Phase I Trial of Intravenous Administration of PV701, an Oncolytic Virus, in Patients with Advanced Solid Cancers" attached to the response dated April 10, 2003. The Pecora article shows the results of a Phase I trial where patients with tumors were treated by intravenous administration of PV 701 (triple plaque purified Mass MK107) as a single dose or in multiple doses. This evidence of successful results (including tumor regression and freedom from tumor progression) with systemic administration confirms the statement of applicants in the subject application that systemic administration as a single dose or as multiple doses, can be used in accordance with the claimed method.

Multiple Doses

On page 13 of the specification, it is stated: " It is also understood that it may be necessary to give more than one dose of the virus." See also Example 2 where multiple systemic doses were given. In this example, complete tumor regressions were noted in 3 out of 4 mice treated multiple times.

Tumor R gressi n

Support for the phrase "tumor regression" can be found throughout the specification, e.g. Example 2. Support for the dosages specified in dependent claims 342, 351 and 352 can be found on page 13 and in Example 2.

With regard to the enablement rejection, 35 USC 112, first paragraph, has no requirement that every embodiment of a claim be exemplified. Claims 332-355 are enabled for the reasons discussed above. The description in the subject specification, the examples therein, as well as subsequent data discussed above, establish that the currently pending claims are sufficiently enabled, i.e. a skilled person would know how to make and use NDV for the claimed use. Likewise, claims 332-355 satisfy the written description requirement of 35 USC 112, first paragraph, for the above-discussed reasons.

Withdrawal of the 35 USC 112, first paragraph, lack of enablement and written description rejections is now in order. Such action is respectfully requested.

V. THE ANTICIPATION REJECTIONS

Claims 318, 320, 322, 323 and 328 stand rejected under 35 USC 102(b) as allegedly anticipated by Lorence et al (1988). Claims 318, 320, 322, 323 and 328 stand rejected under 35 USC 102(a) as allegedly anticipated by Reichard et al (1992). Claims 318, 320, 322, 323 and 328 stand rejected under 35 USC 102(b) as allegedly anticipated by Reichard et al (1992).

In response, and without conceding to the merit of the rejections, claims 318, 320, 322, 323 and 328 have been cancelled without prejudice. Pursuant to the request

during the interview, a brief history of the prior art rejections in the case is presented below, as they pertained to claims similar to currently pending claims.

Previous Prior Art Rejections

In the Official Action dated July 8, 1997, the Examiner rejected claims 164, 165 and 177 under 35 USC 102(b) as being anticipated by Bohle et al., Cassel et al., or Murray et al. Applicants responded in an Amendment dated January 8, 1998, noting that each of these references involves the administration of virus and tumor cells to boost an immune response against antigens present on the tumor cells. The administration in these references was not *systemic administration*. Those 102 rejections were not repeated in the next Official Action (May 26, 1998).

In the Official Action dated May 26, 1998, claims 164, 165, 167, 168 and 177 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lorence et al (1988). Lorence et al discusses *in vitro* tumor cell data, but it contains no *in vivo* data, and no discussion of systemic administration as required by the currently pending claims, dosage or multiple doses.

The January 4, 1995 Action rejected claims 1-4 under 35 U.S.C. §103 as being unpatentable over Reichard (1992). In reply, a declaration by Robert Lorence (pursuant to *In re Katz*) was submitted on June 30, 1995, to which the Examiner responded, in her Official Action dated October 18, 1995 at page 4: "The Lorence Declaration is acknowledged, The Katz declaration is sufficient to remove the Reichard et al reference." In view of the Katz declaration, applicants respectfully submit that the rejection under 35 U.S.C. §102(a) based on Reichard (1992) set forth in the February 10, 2003 Office Action is improper and should be withdrawn.

With regard to the 35 USC 102(b) rejection over Reichard et al, attached is a declaration, dated December 15, 2003, executed by Kirk W. Reichard (joint applicant of the present application and joint author on the Reichard et al paper. The apparent reason the Office has cited Reichard (1992) as a Section 102(b) reference, despite the fact that it appears to have been published less than one year before the April 30, 1993 priority date of the subject application, can be found in the January 4, 1995 Office Action which stated, "It is noted that although Reichard et al appears in the Journal of Surgical Research in May of 1992, the paper was presented at the Annual Meeting of the Association for Academic Surgery in November of 1991", (January 4, 1995 Office Action, page 6). This allegation appears to be based on the fact that the Reichard (1992) paper bears the caption "Presented at the Annual Meeting of the Association for academic Surgery, Colorado Springs, Colorado, Nov. 20-23, 1991", which is more than one year before the April 30, 1993 priority date of the subject application (note: the caption "Presented at the Annual Meeting of the Association for academic Surgery, Colorado Springs, Colorado, Nov. 20-23, 1991" was a generic caption found on papers presented at this meeting). The enclosed declaration of Dr. Reichard explains why Reichard et al is not a Section 102(b) reference against the presently claimed invention. In his declaration Dr. Reichard states, "To the best of my recollection, at no time during my presentation at the [November 20-23, 1991] Colorado meeting . . . did I discuss treatment of cancer by systemic administration of a Newcastle Disease Virus." (Declaration, paragraph 5). Dr. Reichard notes in paragraph 6 of his declaration that while the Reichard et al paper makes reference to systemic treatment (see, towards the bottom of the left hand column on page 452), that language was included for the first

time in the Reichard et al paper when it was initially prepared after the Colorado meeting on November 20-23, 1991.

The Examiner's attention is also directed to the article by Schirrmacher et al (2001) entitled "Antitumor effects of Newcastle Disease Virus in vivo: local versus systemic effects", a copy of which was attached to the response dated April 10, 2003. In the article, the authors note "Systemic anti-metastatic effects were never observed with NDV alone in contrast to previous results obtained with NDV modified tumor vaccines." This article teaches away from the claims of the present application.

As the cited references either do not disclose (or suggest) the systemic administration methodology as claimed in claims 332-355, or are not available as citable prior art, it is clear that all of the outstanding anticipation rejections should be withdrawn. Such action is respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

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